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L8: Entry 11 of 18 File: USPT Oct 9, 2001

DOCUMENT-IDENTIFIER: US 6300118 B1
TITLE: Plasmids comprising a genetically altered feline immunodeficiency virus genome

Abstract Text (1):
The present invention pertains to the prevention or lessening of disease in cats caused by Feline Immunodeficiency Virus (FIV). Prevention or lessening of disease is understood to mean the amelioration of any symptoms, including immune system disruptions, that result from FIV infection. The invention provides for a plasmid which encodes the FIV genome where said genome has had a portion of the gag gene, specifically the p10 (nucleocapsid) coding region, or a portion thereof, deleted. This deletion prevents the production of functional or whole p10 protein, which in turn, prevents the packaging of RNA into virions produced from transfection of this plasmid into an appropriate host cell, resulting in virions which do not contain RNA. Such virions will be described as "empty" virions. The invention also encompasses host cells transformed with the plasmid which produce the empty virions, and the empty virions themselves. In another embodiment, the invention encompasses vaccines that comprise one or more empty virions described above, with a pharmaceutically acceptable carrier or diluent and a pharmaceutically acceptable adjuvant. In yet another aspect, the invention provides methods for preventing or lessening disease caused by FIV, which is carried out by administering to a feline in need of such treatment the vaccines described above.

Brief Summary Text (12):
The invention provides for a plasmid which encodes the FIV genome where said genome has had a portion of the gag gene, specifically the p10 (nucleocapsid) coding region, or a portion thereof, deleted. This deletion prevents the production of functional or whole p10 protein, which in turn, prevents the packaging of RNA into virions produced from transfection of this plasmid into an appropriate host cell, resulting in virions which do not contain RNA. Such virions will be described as "empty" virions. The invention also encompasses host cells transformed with the plasmid which produce the empty virions, and the empty virions themselves.

Detailed Description Text (5):
Although this particular construct and method are effective in producing empty virions, i.e., those which do not contain RNA, one of ordinary skill in the art would recognize alternative well-known methods of achieving the same goal. For example, the deletion need not eliminate the whole p10 encoding sequence, only enough sequence for the function of the protein to be eliminated. One representative example of this approach would be deletion of only one of the two cysteine arrays. Further, fragments of sequence need not be deleted. Any genetic alteration, i.e., site-directed mutagenesis of cysteines within the array, using methods well known in the art can be employed to construct a FIV genome which encodes empty virions. Thus, well-known variants of the genetic alterations presently employed which result in genomes which encode empty virions are contemplated to be within the scope of the present invention.

Detailed Description Text (37):
Fragment E and fragment B generated are purified as above. Then fragment E and fragment B are combined and cloned into the SalI site of the gene targeting vector pMC1neo Poly A (Stratagene, LaJolla, Calf.; Thomas, K. R., and Capecchi, M. R., Cell 51: 503-21, 1987), generating plasmid pFIV delta p10. The plasmid pFIV delta p10 contains the entire FIV genome with internal deletion within the p10 gene in addition

• to the neomycin resistance gene present on the gene targeting vector.

CLAIMS:

1. A plasmid comprising an FIV genome, said genome having a deletion of a region encoding the nucleocapsid (p10) protein; said plasmid comprising:

(a) a deletion of both of the nucleocapsid (p10) protein cysteine arrays, wherein said deletion encompasses nucleotides which result in the deletion of amino acids 14-52 of the FIV p10 protein upon translation,

(b) a gag gene open reading frame, and

(c) a gag-pol frameshift start site; and

where upon transfection of said plasmid into host cells, said host cells have the properties of:

(i) forming non-infectious virions and

(ii) generating stable cell lines of said transfected host cells.

3. Host cells which are transfected with a plasmid comprising an FIV genome, said genome having a deletion of both of the nucleocapsid (p10) regions encoding the nucleocapsid (p10) protein cysteine arrays such that said cells produce FIV virions which do not comprise whole p10 nucleocapsid protein; said plasmid comprising:

(a) a deletion of both of the nucleocapsid (p10) protein cysteine arrays, wherein said deletion encompasses nucleotides which result in the deletion of amino acids 14-52 of the FIV p10 protein upon translation,

(b) a gag gene open reading frame, and

(c) a gag-pol frameshift start site; and

where upon transfection of said plasmid into host cells, said host cells have the properties of:

(i) forming non-infectious virions; and

(ii) generating stable cell lines of said transfected host cells.

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L8	L7 same l5	18	L8
L7	dele$ or muta$	323507	L7
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L5	l4 with l3	99	L5
L4	genome or vector	286486	L4
L3	l2	956	L3
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L1	fiv biv or caev or mvv or EIAV	439	L1

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L8: Entry 4 of 18 File: USPT Apr 29, 2003

DOCUMENT-IDENTIFIER: US 6555107 B2
TITLE: Lentiviral nucleic acids and uses thereof

Detailed Description Text (5):
A "packaging defect which blocks self packaging" of a non-primate lentiviral vector nucleic acid is an inability of the nucleic acid to produce at least one viral protein necessary for packaging the vector nucleic acid into a viral particle in the context of a cell. For example, when Gag or Env proteins are not encoded by the lentiviral vector, the proteins must be supplied in trans before the vector nucleic acid can be packaged in the cell. The omission can be a deletion or mutation of a gene necessary for viral packaging from a viral clone, in the coding or non-coding (e.g., promoter) region of the relevant gene. The vector nucleic acid is trans-rescuable when it encodes a viral packaging site which is recognized be a non-primate lentiviral vector such as FIV.

Detailed Description Text (28):
Transfection of the non-primate lentiviral clone CF1 into human HeLa, 293 and 293-T kidney cells by the calcium phosphate co-precipitation method produced the surprising result of widespread ballooning syncytia (multi-nucleated giant cells produced by fusion of envelope-expressing cells with other cells) containing fifty to several hundred nuclei and high levels (over one million cpm) of supernatant reverse transcriptase. Unexpectedly, human 293 and 293-T cell and HeLa monolayer cultures were reproducibly 90-95% destroyed by syncytia after transient transfection of CF1 (for example by transfection of 10 .mu.g of CF1 in a 75 cm.sup.2 flask), yet, no infectious or replication-competent virus was produced: transfer of large volumes of CF1-transfected 293-T cell supernatant to fresh 293 or 293-T cells or to Crandall feline kidney cells resulted in no syncytia or RT production. CF1.DELTA.env, which is identical to CF1 except for an FIV envelope deletion does not cause syncytia but does produce high levels of reverse transcriptase and of viral functions needed for packaging of vectors. These unprecedented results produced the novel insight that all the functions of non-primate vectors such as FIV needed for protein production, including the Rev/RRE axis of regulation, FIV gag/pol production and envelope-mediated syncytia, could take place in human cells if the FIV promoter were replaced with a promoter active in human cells.

Detailed Description Text (30):
The mechanisms of the FIV life cycle in human cells are described herein. It is reported here for the first time that Feline immunodeficiency virus (FIV) proteins encoded by a packaging plasmid can be expressed at high levels in human cells, in replication-defective fashion, and supplied to FIV packagable vectors in trans, by replacing the long terminal repeat of the FIV genome with a heterologous promoter such as the human cytomegalovirus immediate early promoter (CMV promoter). In particular, substitution of a heterologous polI II promoter for the promoter elements of the FIV LTR enabled high-level FIV protein production, in trans, in human cells. In addition, selectively replacing the FIV 5-prime U3 element by precisely fusing a heterologous promoter to the R repeat resulted in high production in human cells of wild type FIV that was replication-competent only in feline cells. A three plasmid, replication-defective, env-deleted, fully heterologously-promoted FIV vector system was constructed and found to efficiently transduce dividing and non-dividing human cells with vesicular stomatitis virus glycoprotein G (VSV-G)-pseudotyped FIV particles. There was no transduction advantage to feline cells; relative transduction efficiencies in dividing cells of diverse human and feline lineages were the same as

for a Moloney murine leukemia virus (M-MuLV)-based vector. In distinct contrast to the common M-MuLV vector, FIV vectors efficiently transduced non-dividing human cells, including terminally differentiated human macrophages and neurons (hNT neurons). Extensive syncytia form when FIV expression is enabled in human cells; this activity requires expression of CXCR4/fusin35, the co-receptor for syncytium-inducing HIV isolates. Expression of human CXCR4 in feline CRFK cells changes viral phenotype to highly syncytium-inducing and mediates FIV-enveloped vector entry. The studies show that FIV can utilize the human homologue of CXCR4 for syncytiagenesis in human, rodent, and feline cells and, consistent with a co-receptor role, for viral entry in feline cells.

Detailed Description Text (117):
FIV clone 34TF10 was chosen for this work because this FIV clone already has a mutation inactivating the ORF2 gene. See, Talbott, R. L. et al. (1989) Proc. Natl. Acad. Sci. USA 86, 5743-5747. ORF2 is a putative transactivator, which has been shown to be necessary for replication in feline peripheral blood lymphocytes. Thus 34TF10 is an attenuated virus; this attenuation is beneficial for this invention as it further minimizes the risk of wild-type pathogenic FIV while not affecting the vector performance. However, other clones with similar properties are available or can easily be derived by similarly inactivating the wild-type virus using recombinant methods.

Detailed Description Text (118):
Transfection of CF1 into human HeLa, 293 and 293-T kidney cells by the calcium phosphate co-precipitation method produced the surprising result of widespread ballooning syncytia (multi-nucleated giant cells produced by fusion of envelope-expressing cells with other cells) containing fifty to several hundred nuclei and high levels (over one million cpm) of supernatant reverse transcriptase. In fact, we found that human 293 and 293-T cell and HeLa monolayer cultures were reproducibly 90-95% destroyed by syncytia after transient transfection of CF1 (for example by transfection of 10 .mu.g of CF1 in a 75 cm.sup.2 flask), yet as designed and expected, no infectious or replication-competent virus is produced: transfer of large volumes of CF1-transfected 293-T cell supernatant to fresh 293 or 293-T cells or to Crandall feline kidney cells resulted in no syncytia or RT production. CF1.DELTA.env, which is identical to CF1 except for an FIV envelope deletion (see, details below), does not cause syncytia but does produce high levels of reverse transcriptase and of viral functions needed for packaging of vectors. This unprecedented result produced the novel insight that all the functions of FIV needed for protein production, including the Rev/RRE axis of regulation, FIV gag/pol production and envelope-mediated syncytia, can take place in human cells if the FIV promoter is specifically replaced with a promoter active in human cells.

Detailed Description Text (124):
In a preferred embodiment, it was decided to completely replace the promoter function of the FIV U3 in this system (that is, in both packaging and vector constructs) for several reasons (U3, or 3-prime unique region, contains the promoter/enhancer elements of a retrovirus). First, the FIV LTR is inactive or poorly active in human cells and it was desired to attempt production of a vector in human cells since that could increase the likelihood of subsequent human cell transduction and because good transfection systems using feline cells are not well-characterized. Second, the well-known high levels of expression directed by a promoter such as the hCMV immediate early promoter in defined systems (e.g., the 293T human embryonic kidney cell system) are desirable. Third, replacing U3 in both vector and packaging construct will further help to eliminate the risk of replication-competent FIV. In another modification 80 bases of the 3-prime U3 region was also deleted from the vector, including especially the TATA box. Therefore, replication-competent FIV cannot be regenerated because of this deletion, and because the packaging plasmid has both the env gene deletion and the ORF2-inactivating stop codon. Fourth, having all three components (packaging plasmid, vector, envelope-expression plasmid) driven from the same promoter can enhance synchronized expression and efficient particle formation. Fifth, as described above, human cell production is safer than feline cell production for clinical use because feline cells pose the risk of introducing known or unknown infectious agents into humans.

Detailed Description Text (132):
Note that transcription of these vectors occurs from the CMV promoter and not the FIV

promoter. Other promoters are optionally employed. In addition, multiple modifications are possible by deleting additonal regions of the FIV genome, e.g., regions of gag, as detailed below.

Detailed Description Text (134):
1. Vector CTAGCgfsB. The underlined, bold-faced letters in the capsule descriptions, such as the one in parentheses here, indicate the derivation of the name of the vector (CMV promoter joined at TTA box driving expression of an internal reporter gene cassette CMV-GFP-p(A) in reverse orientation and having a gag gene frame shift mutation and subsequent insertion of the sv40T antigen binding site to cause plasmid amplification after transfection in SV40 T antigen-expressing cells). CTAGCgfsB was constructed by three-part ligation of the pvuI-EcoR1 fragment of CT5, the EcoR1-Spe1 fragment of a green fluorescent protein (GFP) gene-containing plasmid, pZcmvGFPpA, and the SpeI-PvuI fragment of CT5. This ligation places the CMV promoter-GFP-p(A) signal cassette in reverse orientation between EcoRI and SpeI in the FIV genome. Next, the Tth III 1 site in the portion of gag/pol remaining in the vector was cleaved, filled in with Klenow polymerase in the presence of 200 .mu.M dNTPs and closed with T4 DNA ligase. This blunting inserts an extra G residue which frameshifts the gag fragment within a few bases of the Tth III 1 site. No pol sequences are present. Therefore, the gag/pol precursor must be supplied in trans from CF1.DELTA.env or subsequent modifications of CF1.DELTA.env. Moreover, this step reduces the chance of wild-type recombination and the chance that a transdominantly-interfering Gag protein fragment will be produced. Finally the sv40-promoter-neoR cassette from pRc/CMV was inserted in the plasmid outside of vector sequences in order to benefit from Sv40 T antigen-driven plasmid amplification and to allow selection for neoR if needed. In one modification, the gag gene ATG start codon can be mutagenized to a stop codon. Also the region between the BsRG1 site and upstream PstI sites is optionally deleted to remove more of gag.

Detailed Description Text (143):
As diagrammed in FIG. 1, the human cytomegalovirus immediate early gene promoter (hCMVIEp) was arranged either (a) to replace all of the FIV LTR with a junction 97 nt upstream of the FIV major 5' splice donor (in plasmid CF1) or (b) to selectively replace the FIV U3 promoter elements (in plasmid CT5, and in FIV vectors) through a fusion at position -14 between the TATA box and the start of transcription, i.e., the R repeat. The arrangement places the CMV TATA box in precise register to the replaced FIV TATA box with respect to the start of transcription (position -27). CF1 lacks both LTRs except for the 89 nt portion of the three-prime U3 that overlaps the rev ORF (FIV has no homologue to HIV nef), thus deleting cis-acting sequences needed for replication and integration (U3 promoter sequences, tRNA primer binding site, R repeats, U5 elements). See also, Example 1 for details of the cloning of the constructs described in this example. CF1.DELTA.env has an additional 875 nt deletion in env which spans the SU-TM junction and is also frameshifting: this plasmid, which was used for packaging of pseudotyped vectors, is thus defective for ORF-2, env, and the cis-acting retroviral elements noted. CT5, in contrast, encodes fully wild-type, replication-competent 34TF10. The system therefore eliminates the need for the feline promoter. The function of ORF2 is not conclusively defined, but FIV LTR-transactivating activity described forits gene product36 would thus also be dispensable.

Detailed Description Text (153):
To examine post-entry phases of the FIV life cycle in human cells, CT5 was used as the starting point for constructing retroviral vectors containing internally promoted marker gene cassettes that replace pol, env and the accessory genes as well as a portion of gag. A frameshift mutation was introduced in all vectors at nt 298 of the remaining gag ORF by blunted closure of a TthIII 1 site, generating a stop codon at nt 319 (FIG. 1). Vector CTRZLb was co-transfected with CF1.DELTA.env and the VSV-G expression plasmid pHCMV-G in 293T cells by calcium phosphate co-precipitation. At 48-96 hours after transfection, supernatants of the FIV vector and of a control VSV-G-pseudotyped Mu-MLV lacZ vector were cleared, filtered (0.45 .mu.M), titered on HeLa cells and then re-titered by limiting dilution on a panel of feline and human cell lines; the experiments were done with cells that were either growing or arrested in G1/S with aphidicolin at 20 .mu.g/ml. High titers (10.sup.6) equivalent to those of a conventional Moloney murine leukemia virus retroviral vector were achievable with a single round of concentration (Burns et al. (1993) Proceedings of the National Academy

of Sciences of the United States of America 90, 8033-8037) by ultracentrifugation. Similar to HIV vectors, the FIV vector was minimally affected by cell cycle arrest, while the Mu-MLV vector transduction was eliminated, thus demonstrating this lentivirus-specific property of the FIV vector and transferablity of this property to human cells. Equally importantly, when compared in growing cells to the VSV-G psudotyped Moloney murine leukemia virus lacZ vector, the FIV vector displayed no significant preference for feline cells (compare titer ratios, see plot in Table inset). When allowed to proliferate after transduction with CTRZLb, large (100-400 cells) homogeneously lacZ-positive colonies were generated, indicating stable, clonal maintenance of the transgene. Although cell lines varied considerably in transducibility as expected, these differences were equivalent for the Moloney and FIV vectors: that is, they were cell-specific rather than vector specific and reflects susceptibility to VSV-G-mediated transduction. The chief block to the infective stage of the FIV life cycle in non-feline cells is thus shown to be at the level of virion entry rather than further downstream.

Detailed Description Text (162):
The results therefore have important implications for lentivirus biology and for human gene therapy. By showing that a non-primate lentivirus also utilizes CXCR-4 for both cell fusion and viral entry, our data show that this chemokine receptor plays a broadly fundamental role in lentivirus replication, in syncytiagenesis, and perhaps in pathogenesis. It is also likely that in vivo replication of FIV has additional and more subtle requirements. FIV vectors therefore represent an inherently safer alternative to HIV vectors. Epidemiologic support for this hypothesis is strongest for FIV than for any other non-primate lentivirus, because FIV has shown no ability to infect or cause disease in humans after natural inoculation in many humans over many years by the same principal infective route operative in cats (cat bites). Furthermore, in addition to U3, ORF2 and env, additional deletions of FIV sequences from both vectors and packaging plasmids are possible. FIV vectors are logistically easier to produce since infectious FIV is routinely propagated in Biosafety Level 2 tissue culture (vectors herein are approved for BL-2 use by the UC San Diego Institutional Biosafety Committee).

(FILE 'MEDLINE, EMBASE, CANCERLIT, BIOTECHDS, BIOSIS' ENTERED AT 17:40:17 ON 15 OCT 2003)

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                DEL HIS
L1           969 S EIAV
L2        295034 S DELETION OR DELETED
L3         19396 S TAT
L4           998 S L3 AND L2
L5            22 S L4 AND L1
L6             8 DUP REM L5 (14 DUPLICATES REMOVED)
L7            52 S NON-PRIMATE AND LENTIVI?
L8             4 S L2 AND L7
L9             4 DUP REM L8 (0 DUPLICATES REMOVED)
L10       858541 S MUTAT?
L11            3 S L10 AND L7
L12         3294 S FIV
L13      1051775 S L2 OR L10
L14          155 S L13 AND L12 AND L2
L15           11 S L14 AND L3
L16            5 DUP REM L15 (6 DUPLICATES REMOVED)
L17       278272 S GENOME
L18       306659 S VECTOR
L19          112 S L1 AND L18
L20           15 S L19 AND L13
L21            8 DUP REM L20 (7 DUPLICATES REMOVED)
L22          267 S L12 AND L18
L23           49 S L22 AND L13
L24           33 DUP REM L23 (16 DUPLICATES REMOVED)
L25            2 S L24 AND L3
L26          183 S L12 AND L17
L27           49 S L26 AND L13
L28            1 S L27 AND L3
L29        31938 S DELIVERY AND TRANSFE?
L30            0 S L27 AND L29
L31           42 S L22 AND L29
L32           27 DUP REM L31 (15 DUPLICATES REMOVED)
L33         2472 S BIV OR CAEV OR MVV
L34          235 S L33 AND (L17 OR L18)
L35           38 S L34 AND L13
L36            2 S L35 AND L29
L37            2 DUP REM L36 (0 DUPLICATES REMOVED)
L38           19 DUP REM L35 (19 DUPLICATES REMOVED)
L39          218 S L1 AND (L17 OR L18)
L40           48 S L39 AND L13
L41           23 DUP REM L40 (25 DUPLICATES REMOVED)

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L41 ANSWER 14 OF 23 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 96161286 EMBASE
DN 1996161286
TI Inhibitory activity of the equine infectious anemia virus major 5' splice site in the absence of Rev.
AU Tan W.; Schalling M.; Zhao C.; Luukkonen M.; Nilsson M.; Fenyo E.M.; Pavlakis G.N.; Schwartz S.
CS Microbiology and Tumorbiology Center, Karolinska Institute, P.O. Box 280,171 77 Stockholm, Sweden
SO Journal of Virology, (1996) 70/6 (3645-3658).
ISSN: 0022-538X CODEN: JOVIAM
CY United States
DT Journal; Article
FS 004 Microbiology
LA English
SL English
AB The major 5' splice site of equine infectious anemia virus (**EIAV**) conforms to the consensus 5' splice site in eight consecutive positions and is located immediately upstream of the gag AUG. Our results show that the presence of this 5' splice site on the **EIAV** gag mRNA decreases Gag production 30- to 60- fold. This is caused by inefficient nuclear mRNA export and inefficient mRNA utilization. Inhibition could be overcome by providing human immunodeficiency virus type 1 Rev/Rev-responsive element, human T-cell leukemia virus type 1 Rex/Rex-responsive element, or simian retrovirus type 1 constitutive transport element. In addition, inhibition could be abolished by introducing single point **mutations** in the 5' splice site or by moving the 5' splice site away from its natural position immediately upstream of the gag AUG. This demonstrates that both maintenance of a perfect consensus 5' splice site and its proper location on the mRNA are important for inhibitory activity of the **EIAV** major 5' splice site.

L41 ANSWER 22 OF 23 MEDLINE on STN DUPLICATE 11
AN 88062973 MEDLINE
DN 88062973 PubMed ID: 2824840
TI Localization of sequences responsible for trans-activation of the equine infectious anemia virus long terminal repeat.
AU Sherman L; Gazit A; Yaniv A; Kawakami T; Dahlberg J E; Tronick S R
CS Department of Human Microbiology, Sackler Faculty of Medicine, Tel-Aviv University, Israel.
SO JOURNAL OF VIROLOGY, (1988 Jan) 62 (1) 120-6.
Journal code: 0113724. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 198801
ED Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19880121
AB We used the Escherichia coli chloramphenicol acetyltransferase gene (cat) to study sequences that influence expression of the equine infectious anemia virus (**EIAV**) **genome**. The **EIAV** long terminal repeat (LTR) directed CAT activity in a canine cell line, but at levels much lower than those achieved with other eucaryotic viral promoters. In the same cells infected with **EIAV** or cotransfected with molecularly cloned **EIAV** genomic DNA, LTR-directed activity was markedly enhanced. Comparison of cat mRNA and protein levels in these cells indicated that this trans-activating effect could be accounted for by a bimodal mechanism in which both transcriptional and posttranscriptional events are enhanced. trans-Activation but not promoter activity was abolished by **deletion** of the R-U5 region of the **EIAV** LTR. **EIAV** sequences responsible for the trans-activating function could be localized to a region encompassing the 3' and 5' termini of the pol and env genes, respectively (nucleotides 4474 to 5775). Interestingly, this stretch harbors a short open reading frame with some amino acid sequence similarity to the human immunodeficiency virus type I tat gene product.

L41 ANSWER 23 OF 23 MEDLINE on STN DUPLICATE 12
AN 87236196 MEDLINE
DN 87236196 PubMed ID: 3035786
TI Nucleotide sequence analysis of equine infectious anemia virus proviral DNA.
AU Kawakami T; Sherman L; Dahlberg J; Gazit A; Yaniv A; Tronick S R; Aaronson S A
SO VIROLOGY, (1987 Jun) 158 (2) 300-12.
Journal code: 0110674. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
OS GENBANK-K03334; GENBANK-M11337; GENBANK-M14855; GENBANK-M16575
EM 198707
ED Entered STN: 19900305
Last Updated on STN: 19970203
Entered Medline: 19870701
AB The nucleotide sequence of the integrated form of the **genome** of the equine infectious anemia virus was determined. By comparison with LTR sequences of other retroviruses, signals for the control of viral gene transcription and translation could be identified in the **EIAV** LTR. Open reading frames for gag and pol genes were identified and their sequences matched very closely to those determined previously by others. However, in the present study, the pol gene reading frame was open throughout its entire length. The open reading frame for the env gene product was constructed from the sequences of two independent **EIAV** clones. Thus, a noninfectious genomic-length clone was shown to contain a frameshift **mutation** approximately in the middle of the presumed env gene coding sequence, whereas the sequence of another clone was open in this region. The deduced amino acid sequences of the **EIAV** gag and pol products showed closer evolutionary relationships to those of known lentiviruses than to other retroviruses. There was also partial sequence homology between predicted env gene products of **EIAV**, visna virus, and HTLV-III/LAV. Sequences analogous to the sor region of other lentiviruses could not be identified in our **EIAV** clone. A short open reading frame at the 3' end of the **genome** that overlapped env but not the 3' LTR was present but lacked significant sequence similarity to the 3' open reading frames of other lentiviruses. Thus, the sequence and general structure of **EIAV** most closely resemble those of known lentiviruses.

L38 ANSWER 6 OF 19 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
AN 2000-03590 BIOTECHDS
TI Live attenuated feline immunodeficiency virus useful as a vaccine to immunize hosts against feline immunodeficiency virus;
attenuated HIV virus, FIV virus, **BIV** virus, SIV virus, etc., recombinant vaccine
AU Luciw P A; Sparger E E
PA Univ.California
LO Oakland, CA, USA.
PI US 6004799 21 Dec 1999
AI US 1997-811828 5 Mar 1997
PRAI US 1997-811828 5 Mar 1997
DT Patent
LA English
OS WPI: 2000-072063 [06]
AB A non-natural FIV virus (I) derived from a pathogenic FIV virus by specifically mutagenizing or deleting one or more of its genes or genetic elements responsible for pathgenicity is claimed. (I) is attenuated in pathogenicity and elicits an immune response against a pathogenic FIV virus in a host inoculated with (I). Also claimed are: a non-naturally occurring FIV virus **vector** (II) with one or more of its genes or genetic elements responsible for pathogenicity specifically removed or inactivated, that is attenuated in pathogenicity and able to prevent or delay infection of a host by, or limit dissemination and establishment of a pathogenic FIV virus in a host inoculated with the non-natural FIV virus; therapy or immunization of an animal against infection by FIV virus or its related pathogen involving administering (I) or the **vector** (II); a **vector** derived from (I); a provirus construct driven by SV40pr/RU5 promoter; and a vaccine comprising the self-replicating provirus DNA construct including the whole **genome** of an animal lenti virus with at least one **mutation** or **deletion** in a region responsible for transcription, initiation or multiplication. (27pp)

L38 ANSWER 9 OF 19 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
AN 1997-12701 BIOTECHDS
TI Attenuated feline immunodeficiency virus and vectors useful in vaccines; recombinant vaccine against FIV virus, HIV virus, **BIV** virus, SIV virus, visna virus, horse infectious-anemia virus or goat arthritis-encephalitis virus infection
AU Luciw P A; Sparger E E
PA Univ.California
LO Oakland, CA, USA.
PI WO 9732983 12 Sep 1997
AI WO 1997-US4138 5 Mar 1997
PRAI US 1996-611321 5 Mar 1996; US 1996-691662 2 Aug 1996
DT Patent
LA English
OS WPI: 1997-470547 [43]
AB A non-natural FIV virus which has at least 1 gene or genetic element required for pathogenicity absent or partly non-functional and which is able to elicit an immune response in its infected host is claimed. Also claimed are: non-natural FIV virus vectors which have at least 1 gene or genetic element required for pathogenicity absent or partly non-functional; FIV pro virus constructs or virus driven by the SV40 virus pr/RU5 promoter (A); a vaccine comprising self-replicating pro virus DNA including almost the whole of a lenti virus **genome** with at least 1 **mutation** in a region responsible for regulation, initiation or multiplication. The FIV viruses and vectors are useful as live, attenuated vaccines to treat or prevent infections by FIV virus or related viruses, especially in cats. The vaccines are used similarly against HIV virus, SIV virus, **BIV** virus, horse infectious-anemia virus, visna virus or goat arthritis-encephalitis virus. A protective response, preferably both cellular and humoral, is achieved after a single immunization. (66pp)

L38 ANSWER 11 OF 19 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
AN 1995-15185 BIOTECHDS
TI Packaging-deficient lenti virus;
vector composed of antisense DNA for Maedi-Visna virus and HIV virus-2 expression inhibition, for application in gene therapy
AU Lever A M L; Harrison G P; Hunter E
PA Syngenix
PI WO 9525806 28 Sep 1995
AI WO 1995-GB663 24 Mar 1995
PRAI GB 1994-25026 9 Dec 1994; GB 1994-5875 24 Mar 1994
DT Patent
LA English
OS WPI: 1995-344622 [44]
AB A **vector** that is capable of producing proteins of a virus selected from Maedi-Visna virus (**MVV**) and HIV virus-2, but not of packaging the viral RNA, is new. Preferably, the **vector** has a **deletion** corresponding to that between the major splice site and the gag initiation codon. It is capable of producing lenti virus protein, and is modified by **deletion** or other non-functionalization of a stem-loop structure composed of a GAYC motif or of G:C pairs terminating in a loop containing an ACC motif. The **vector** is composed of lenti virus packaging nucleotides, a heterologous gene, and flanking these, sequences corresponding to those within and near the virus long terminal repeats sufficient for packaging, reverse transcription and integration of the **vector** into target cells, to enable expression of the heterologous gene. The integrating sequence encodes the matrix protein and it may also comprise the integrase protein sequence. The **vector** may be used for the integration of foreign DNA into a non-dividing cell in gene therapy. The **vector** may especially be used to carry antisense DNA to regions of the **MVV** or HIV virus-2 **genome** to inhibit lenti viral replication. (20pp)

L38 ANSWER 12 OF 19 MEDLINE on STN
AN 95363954 MEDLINE
DN 95363954 PubMed ID: 7636990
TI The caprine arthritis encephalitis virus tat gene is dispensable for efficient viral replication in vitro and in vivo.
AU Harmache A; Vitu C; Russo P; Bouyac M; Hieblot C; Peveri P; Vigne R; Suzan M
CS Institut National de la Sante et de la Recherche Medicale, U372, Marseille, France.
SO JOURNAL OF VIROLOGY, (1995 Sep) 69 (9) 5445-54.
Journal code: 0113724. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199509
ED Entered STN: 19950921
Last Updated on STN: 19970203
Entered Medline: 19950914
AB Caprine arthritis encephalitis virus (**CAEV**) is a lentivirus closely related to visna virus and more distantly to other lentiviruses, such as human immunodeficiency virus. The genomes of visna virus and **CAEV** contain a tat gene encoding a protein able to weakly transactivate its own long terminal repeat, suggesting that transactivation may be a dispensable function for viral replication. Three different tat gene mutants of an infectious molecular clone of **CAEV** were used to study their replication after transfection or infection of primary goat synovial membrane cells and of blood-derived mononuclear cells or macrophages. Our results showed no difference between replication of the wild type and either the complete tat **deletion** mutant or the tat stop point mutant, whereas slower growth kinetics and lower levels of expression of the partial tat **deletion** mutant that of the wild type were obtained in these cells. Quantitative PCR and reverse transcription-PCR analyses of the different steps of a single replicative cycle revealed an identical pattern of retrotranscription, transcription, and viral production, whereas time course analysis demonstrated that the intracellular level of viral genomic RNA was affected by the partial tat **deletion** at later time points. We then compared the infectious properties of the wild-type and tat mutant viruses in vivo by direct inoculation of proviral DNAs into the joints of goats. All the animals seroconverted between 27 and 70 days postinoculation. Moreover, we were able to isolate tat mutant **CAEV** from blood-derived macrophages that was still able to infect synovial membrane cells in vitro. This study clearly demonstrates that the tat gene of **CAEV** is dispensable for viral replication in vitro and in vivo.

L38 ANSWER 13 OF 19 MEDLINE on STN DUPLICATE 5
AN 95297130 MEDLINE
DN 95297130 PubMed ID: 7778264
TI Erratic G-->A hypermutation within a complete caprine arthritis-encephalitis virus (**CAEV**) provirus.
AU Wain-Hobson S; Sonigo P; Guyader M; Gazit A; Henry M
CS Unite de Retrovirologie Moleculaire, Institut Pasteur, Paris, France.
SO VIROLOGY, (1995 Jun 1) 209 (2) 297-303.
Journal code: 0110674. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199507
ED Entered STN: 19950720
Last Updated on STN: 19950720
Entered Medline: 19950711
AB The complete nucleotide sequence of an integrated provirus of caprine arthritis-encephalitis virus (**CAEV**) has been determined. The provirus was defective due to extensive G-->A hypermutation. Rather than being a smooth phenomenon distributed throughout the **genome** it was highly erratic with hypermutated and normal regions being juxtaposed, probably reflecting local fluctuations in the intracellular dCTP pool during reverse transcription of the **CAEV genome**. The pattern of sequence variation within the surface glycoproteins differs subtly from that of the primate lentiviruses.

L38 ANSWER 15 OF 19 MEDLINE on STN DUPLICATE 7
AN 94279130 MEDLINE
DN 94279130 PubMed ID: 8009824
TI A Rev protein is expressed in caprine arthritis encephalitis virus (**CAEV**)-infected cells and is required for efficient viral replication.
AU Schoborg R V; Saltarelli M J; Clements J E
CS Johns Hopkins University School of Medicine, Baltimore, Maryland 21205.
NC AI 28748 (NIAID)
NS 23039 (NINDS)
T32 A107394
SO VIROLOGY, (1994 Jul) 202 (1) 1-15.
Journal code: 0110674. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199407
ED Entered STN: 19940729
Last Updated on STN: 19940729
Entered Medline: 19940715
AB Caprine arthritis encephalitis virus (**CAEV**) is a lentivirus that is closely related to visna virus and more distantly related to the human lentivirus human immunodeficiency virus 1 (HIV-1). Like other lentiviruses, the **genome** of **CAEV** contains multiple small ORFs that encode viral regulatory proteins. Sequence analysis of the **CAEV genome** and cDNAs generated from mRNA in infected cells has suggested that one of these ORFs encodes a protein (Rev-C) that is analogous to Rev of visna virus and HIV. Antibodies generated to a carboxy-terminal peptide of the rev ORF immunoprecipitate an 18-kDa protein from cells transfected with the Rev cDNA clone. Immunoprecipitation and immunofluorescence analysis of **CAEV** -infected ovine primary cells show that the product of the rev ORF is expressed during infection and localizes to the nucleolus of infected cells. Also, sera from **CAEV**-infected goats specifically immunoprecipitates an in vitro-translated product from the full-length Rev cDNA clone as well as that from the unique second open reading frame of Rev-C which shows that the Rev-C protein is expressed during natural **CAEV** infection of animals. Insertion of either a **mutation** that creates two stop codons in the unique second open reading frame of Rev-C or a **mutation** in the basic domain of Rev-C into the **CAEV** infectious molecular clone renders the virus unable to replicate in primary goat synovial membrane cells. Analysis of the RNA and proteins produced from both Rev-deficient clones indicates that they are defective in the accumulation of structural gene mRNAs in the cytoplasm as well as in synthesis of structural proteins compared to the wild-type **CAEV** clone. These data indicate that **CAEV** encodes a Rev protein that is required for efficient viral replication in culture.

L38 ANSWER 16 OF 19 MEDLINE on STN DUPLICATE 8
AN 94025584 MEDLINE
DN 94025584 PubMed ID: 8212571
TI The **CAEV** tat gene trans-activates the viral LTR and is necessary for efficient viral replication.
AU Saltarelli M J; Schoborg R; Gdovin S L; Clements J E
CS Frederick Cancer Research and Development Center, Department of Human Retrovirus, Maryland 21702.
NC AI27297 (NIAID)
AI28748 (NIAID)
NS23039 (NINDS)
SO VIROLOGY, (1993 Nov) 197 (1) 35-44.
Journal code: 0110674. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199311
ED Entered STN: 19940117
Last Updated on STN: 19940117
Entered Medline: 19931122
AB Caprine arthritis-encephalitis virus (**CAEV**) is a lentivirus which is closely related by nucleotide sequence and biological properties to visna virus. Sequence analysis of the **CAEV genome** revealed the presence of a small open reading frame (ORF) which shares amino acid identity with the visna virus tat gene. Using an infectious molecular clone of **CAEV** the role of the tat ORF in viral replication was examined. **Mutations** were made in the tat ORF that introduced two in frame stop codons six amino acids downstream of the tat AUG; in addition, a **deletion** mutant was made that removed most of the tat ORF. Both of these mutants had greatly reduced virus titers (> 1000-fold less than the wild type infectious clone). Co-transfection of a tat expressing plasmid with these viruses containing the tat ORF **mutations** resulted in higher levels of virus production demonstrating that the effects of both mutants are tat specific. These mutants provide data that the **CAEV** tat gene is necessary for efficient virus replication. Analysis of the RNA in these transfected cells showed that complementation of the tat gene was in trans and not the result of recombination. Analysis of the gag and rev proteins in the transfected cells demonstrated that these proteins were not detectable in cells transfected with the tat mutants but could be readily detected when the **mutations** were complemented in trans with a tat expression **vector**. To test for tat mediated trans-activation a plasmid expressing the **CAEV** tat ORF was co-transfected with plasmids containing either the **CAEV** or visna virus LTR driving transcription of the bacterial chloramphenicol acetyltransferase gene (CAT). These experiments indicate that one function of the **CAEV** tat protein is to trans-activate gene expression from the viral promoter. RNase protection analysis of CAT mRNA from co-transfected cells demonstrated that **CAEV** Tat trans-activates gene expression by increasing steady-state levels of mRNA.

L38 ANSWER 19 OF 19 MEDLINE on STN DUPLICATE 10
AN 90223985 MEDLINE
DN 90223985 PubMed ID: 2183467
TI Nucleotide sequence and **genome** organization of biologically active proviruses of the bovine immunodeficiency-like virus.
AU Garvey K J; Oberste M S; Elser J E; Braun M J; Gonda M A
CS Laboratory of Cell and Molecular Structure, NCl-Frederick Cancer Research Facility, Maryland 21701.
NC NO1-C0-74102
SO VIROLOGY, (1990 Apr) 175 (2) 391-409.
Journal code: 0110674. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199005
ED Entered STN: 19900622
Last Updated on STN: 19900622
Entered Medline: 19900523
AB The complete nucleotide sequences and translations of major open reading frames (ORF) of two distinct, infectious, proviral molecular clones (106 and 127) of the bovine immunodeficiency-like virus (**BIV**), obtained from a single virus isolation, were determined and compared. The genomes of **BIV** 127 and 106 are 8482 and 8391 nucleotides (nt), respectively, in the form predicted for the viral RNA. The structural organization of the genomes of **BIV** 127 and 106 are identical to one another and most similar to that of the lentivirus subfamily of retroviruses. In addition to gag, pol, and env genes, the **BIV** **genome** contains five short ORFs between and overlapping pol and env in the "central region," a hallmark of the lentiviruses which is believed to play an important role in their pathogenesis. Three of the short ORFs in the central region of **BIV** have been identified by location and structural similarity to the nonstructural/regulatory genes (vif, tat, and rev) of other lentiviruses; we also discovered two unique ORFs, termed W and Y, which may serve as exons for novel genes. **BIV** does not have the nef gene found in primate lentivirus genomes. The proviral LTR of **BIV** 127 is 589 nt, contains regulatory signals for initiation, enhancement, and termination of viral transcription, and has sequences related to the Sp1 and NF-kappa B binding sites. A major **deletion** (87 nt) in the env gene and 2 minor deletions (2 nt each) in the R regions of the LTRs account for the smaller size of clone 106. Numerous point **mutations** were also present; some caused coding substitutions that were most prevalent in the env encoding ORF. These data suggest that, within a single virus isolate, **BIV** displays extensive genomic variation. These infectious clones of **BIV** represent well-defined tools with which to analyze the function of the various ORFs and to dissect the molecular mechanisms of replication and pathogenesis.

L37 ANSWER 2 OF 2 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN 2002332940 EMBASE

TI Development of second- and third-generation bovine immunodeficiency virus-based gene **transfer** systems.

AU Matukonis M.; Li M.; Molina R.P.; Paszkiet B.; Kaleko M.; Luo T.

CS Dr. T. Luo, Genetic Therapy, Inc., Novartis Company, 9 West Watkins Mill Road, Gaithersburg, MD 20878, United States. tianci.luo@pharma.novartis.com

SO Human Gene Therapy, (2002) 13/11 (1293-1303).
Refs: 46
ISSN: 1043-0342 CODEN: HGTHE3

CY United States

DT Journal; Article

FS 004 Microbiology
022 Human Genetics
037 Drug Literature Index
039 Pharmacy

LA English

SL English

AB Lentivirus-based gene **transfer** systems have demonstrated their utility in mediating gene **transfer** to dividing and nondividing cells both in vitro and in vivo. An early-generation gene **transfer** system developed from bovine immunodeficiency virus (**BIV**) has been described (Berkowitz et al., J. Virol. 2001;75:3371 -3382). In this paper, we describe the development of second-generation (three-plasmid) and third-generation (four-plasmid) **BIV**-based systems. All accessory genes (vif, vpw, vpy, and tmx) and the regulatory gene tat were **deleted** or largely truncated from the packaging construct. Furthermore, we split the packaging function into two constructs by expressing Rev in a separate plasmid. Together with our minimal **BIV transfer vector** construct and a vesicular stomatitis virus G glycoprotein-expressing plasmid, the **BIV** vectors were generated. The vectors produced by the three- and four-plasmid systems had titers greater than 1 x 10(6) transducing units per milliliter and were fully functional as indicated by their ability to efficiently transduce both dividing and non-dividing cells. These results suggest that the accessory genes vif, vpw, vpy, and tmx are dispensable for functional **BIV vector** development. The modifications made to the packaging constructs improve the safety profile of the **vector** system. Finally, **BIV** vectors provide an alternative to human immunodeficiency virus-based gene **transfer** systems.

L32 ANSWER 26 OF 27 MEDLINE on STN DUPLICATE 7
AN 1999252191 MEDLINE
DN 99252191 PubMed ID: 10233961
TI Minimum requirements for efficient transduction of dividing and nondividing cells by feline immunodeficiency virus vectors.
AU Johnston J C; Gasmi M; Lim L E; Elder J H; Yee J K; Jolly D J; Campbell K P; Davidson B L; Sauter S L
CS Center for Gene Therapy, Chiron Technologies, San Diego, California 92121, USA.
NC NS34568 (NINDS)
RO1AI25825 (NIAID)
SO JOURNAL OF VIROLOGY, (1999 Jun) 73 (6) 4991-5000.
Journal code: 0113724. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199906
ED Entered STN: 19990618
Last Updated on STN: 19990618
Entered Medline: 19990607
AB The development of gene **delivery** vectors based on feline immunodeficiency virus (**FIV**) is an attractive alternative to vectors based on primate sources for the **delivery** of genes into humans. To investigate the requirements for efficient transduction of dividing and nondividing cells by **vector** particles based on **FIV**, a series of packaging and **vector** constructs was generated for which viral gene expression was minimized and from which unnecessary cis-acting sequences were deleted. Pseudotyped **vector** particles produced in 293T cells were used to transduce various target cells, including contact-inhibited human skin fibroblasts and growth-arrested HT1080 cells. **FIV** vectors in which the U3 promoter was replaced with the cytomegalovirus promoter gave rise to over 50-fold-higher titers than **FIV** vectors containing the complete **FIV** 5' long terminal repeat (LTR). Comparison of the transduction efficiencies of vectors containing different portions of the **FIV** Gag coding region indicates that at least a functional part of the **FIV** packaging signal (Psi) is located within an area which includes the 5' LTR and the first 350 bp of gag. Transduction efficiencies of vectors prepared without **FIV** vif and orf2 accessory gene expression did not differ substantially from those of vectors prepared with accessory gene expression in either dividing or nondividing cells. The requirement for **FIV** rev-RRE was, however, demonstrated by the inefficient production of **vector** particles in the absence of rev expression. Together, these results demonstrate the efficient transduction of nondividing cells in vitro by a multiply attenuated **FIV vector** and contribute to an understanding of the minimum requirements for efficient **vector** production and infectivity. In addition, we describe the ability of an **FIV vector** to deliver genes in vivo into hamster muscle tissue.

L25 ANSWER 1 OF 2 MEDLINE on STN
AN 2003353576 MEDLINE
DN 22768206 PubMed ID: 12885901
TI Feline immunodeficiency virus ORF-Ais required for virus particle formation and virus infectivity.
AU Gemeniano Malou C; Sawai Earl T; Leutenegger Christian M; Sparger Ellen E
CS Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis, California 95616, USA.
NC 5 F31 GM19259-03 (NIGMS)
R01AI40896 (NIAID)
R01AI46145-01A2 (NIAID)
R21AI46276 (NIAID)
SO JOURNAL OF VIROLOGY, (2003 Aug) 77 (16) 8819-30.
Journal code: 0113724. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200309
ED Entered STN: 20030730
Last Updated on STN: 20030924
Entered Medline: 20030923
AB The orf-A (orf-2) gene of feline immunodeficiency virus (**FIV**) is a small open reading frame predicted to encode a 77-amino-acid protein that contains putative domains similar to those of the ungulate lentiviral **Tat** protein. Orf-A is reported to be critical for efficient viral replication in vitro and in vivo. A series of **FIV**-pPPR-derived proviruses with in-frame deletions and point **mutations** within orf-A were constructed and tested for replication in feline lymphoid cells. Orf-A mutant proviruses were also tested for viral gene and protein expression, viral particle formation, and virion infectivity. Deletions within orf-A severely restricted **FIV** replication in feline peripheral blood mononuclear cells (PBMC) and interleukin-2-dependent T-cell lines. In addition, substitutions of alanines for leucines in the putative leucine-rich domain, for cysteines in the putative cysteine-rich domain, and for a tryptophan at position 43 in Orf-A restricted the replication of **FIV** mutants. Deletions and point **mutations** in orf-A imposed a small effect or no effect on **FIV** long-terminal-repeat-driven viral gene expression and had no effect on viral protein expression. However, release of cell-free, virion-associated viral RNA in supernatants from cells transfected with orf-A mutant proviruses was severely restricted but was rescued by cotransfection with a wild-type Orf-A expression **vector**. In addition, virions derived from orf-A mutant proviruses expressed reduced infectivity for feline PBMC. Our findings suggest that Orf-A functions involve multiple steps of the **FIV** life cycle including both virion formation and infectivity. Furthermore, these observations suggest that Orf-A represents an **FIV**-encoded analog more similar to the accessory gene vpr, vpu, or nef than to the regulatory gene **tat** encoded by the primate lentiviruses.

L16 ANSWER 3 OF 5 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
AN 2001-01706 BIOTECHDS
TI New vector system to produce a pseudotyped lenti virus vector which has modifications to enhance safety, useful for delivering a desired gene; HIV virus, **FIV** virus, visna virus and horse infectious-anemia virus production for gene deliver and gene therapy
AU Marasco W A; Ogueta S
PA Dana-Farber-Cancer-Inst.
LO Boston, MA, USA.
PI WO 2000055335 21 Sep 2000
AI WO 2000-US6971 16 Mar 2000
PRAI US 1999-124641 16 Mar 1999
DT Patent
LA English
OS WPI: 2000-647076 [62]
AB A vector system that produces a pseudotyped lenti virus vector that can be used to deliver a desired gene, is new. The vectors within the system contain a **deletion** of the US portion of the lenti virus long terminal repeat sufficient to inactivate the lenti virus promoter and/or do not express a **tat** protein that has transactivating functions. Also claimed is a method of delivering an angiogenic protein to a vascular endothelial cell which involves administering a particle produced by a vector system where the lenti virus is the HIV virus. The lenti virus can also be **FIV** virus, visna virus and horse infectious-anemia virus. The lenti virus particles can be used for gene delivery and transfer of nucleic acid sequences. The molecules encoded for can be proteins such as antibodies, growth factors, receptors, cytokines, peptides and antisense molecules. (75pp)